PROPOSAL FOR TOPIC APPROVAL TO BE SUBMITTED TO THE UNIVERSITY OF MUMBAI FOR THE PH. D DEGREE IN THE SUBJECT OF PHARMACEUTICS

Title of the thesis	Novel strategies in the oral delivery of some antidiabetic drugs
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Topic: Novel strategies in the oral delivery of some antidiabetic drugs

1. Aim

To develop a novel drug delivery system containing Antidiabetic drugs to enhance the bioavailability of poorly water-soluble drugs and reduce the dosing frequency.

2. Objectives of the study

To develop sustained and or extended-release pharmaceutical composition with the desired physical and chemical parameters with an aim to reduce dose, related side-effects, improve patient compliance by improving adherence to dosage regimens.

To improve therapeutic efficacy by improving bioavailability using solubility enhancement techniques.

3. Study Background and Significance

Diabetes mellitus (DM) type 2 also known as type 2 diabetes is a long-term metabolic disorder that is characterized by high blood sugar, insulin resistance, and relative lack of insulin. The development of type 2 diabetes is caused by a combination of lifestyle and genetic factors. While some of these factors are under personal control, such as diet and obesity, other factors are not, such as increasing age, female gender, and genetics. It is estimated that 366 million people had type 2 diabetes mellitus in 2011; by 2030 this would have risen to 552 million. Thus, research for anti-diabetic drugs becomes important as type 2 diabetes is an incredibly prevalent disease in the modern world and new treatment choices are much needed. [1]

An alarmingly low rate of treatment adherence undermines global public health efforts to treat a variety of chronic conditions. Patients on long-term treatment face a serious issue called non-adherence. Patients who do not adhere to treatment may not see the benefits in a sufficient manner. Adherence issues are common in both acute and chronic conditions, including diabetes, where self-administration of treatment is required. Additionally, in settings with limited resources, once-daily dosing may be extremely important. Additionally, the existing formulations have a high dosage regimen and low bioavailability. [2-3]

4. National status

Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease. In 2000, India (31.7 million) topped the world with the highest number of people with diabetes mellitus followed by China (20.8 million) with the United States (17.7 million) in second and third place respectively. According to Wild et al. the prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India. [4]

It is predicted that by 2030 diabetes mellitus may afflict up to 79.4 million individuals in India, while China (42.3 million) and the United States (30.3 million) will also see significant increases in those affected by the disease.3,4 India currently faces an uncertain future in relation to the potential burden that diabetes may impose upon the country. Many influences affect the prevalence of disease

throughout a country, and identification of those factors is necessary to facilitate change when facing health challenges. [4-6]

5. International status

The global oral antidiabetic drugs market is expected to witness significant growth during the forecast period. Increasing cases of type 2 diabetes boosts the oral antidiabetic drugs market. The adaptation of unhealthy lifestyle, environment pollution and family history with diabetes disease also boost up the oral antidiabetic drugs market growth. Many major market players are contributing a lot in drug discovery and development. COVID-19 also had a major impact on the market growth.

Globally, an estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980. The global prevalence (age-standardized) of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population. This reflects an increase in associated risk factors such as being overweight or obese. Over the past decade, diabetes prevalence has risen faster in low- and middle-income countries than in high-income countries. [5-6]

It is clear that though options exist for disorders associated with type-2 DM however, many such treatment options are associated with some or more side effects. Therefore, there is still a need to develop sustained or extended release pharmaceutical composition of Antidiabetic drugs like Dipeptidyl peptidase- IV (DPP-IV), SGLT-2 inhibitors, GLP-1 agonists and or alpha glucosidase inhibitors with satisfactory physical, chemical, desired dissolution profile and stability parameters.[7-10]

6. Study Hypotheses

Hypothesis of current project involves mainly development of a novel oral formulation of drugs with antidiabetic activity. Additionally, the project aims dose reduction and improve patient compliance by improving adherence to dosage regimens. More particularly, the project relates to a sustained and or extended-release dosage form comprising of not much studied antidiabetic drugs like Dipeptidyl peptidase- IV (DPP-IV), SGLT-2 inhibitors, GLP-1 agonists and or alpha glucosidase inhibitors, with desired physical and chemical parameters. Pharmacokinetics and efficacy studies will be performed to check the improved absorption after oral administration.

7. Rationale of the study

7.1 Rationale for selection of drugs and drug delivery systems

The present investigation aims to develop a novel oral formulation of some antidiabetic drugs like DPP4 inhibitors, SGLT2 inhibitors, GLP-1 agonists and or Alpha glucosidase inhibitors to reduce dose, related side-effects, improve patient compliance by improving adherence to dosage regimens. The effective novel oral drug delivery system will be developed to improve therapeutic efficacy by improving bioavailability using solubility enhancement techniques.

Based on the literature it is clear that though options exist for Diabetes treatment however, many such treatment options are associated with some or more side effects. Therefore, there is still a need for an oral formulation containing antidiabetic drugs like DPP4 inhibitors, SGLT2 inhibitors, GLP-1 agonists and or Alpha glucosidase inhibitors. It is desirable to develop sustained and or extended-release pharmaceutical composition of some antidiabetic drugs like DPP4 inhibitors, SGLT2

inhibitors, GLP-1 agonists and or alpha glucosidase inhibitors with satisfactory physical, chemical, desired dissolution profile and stability parameters. The developed novel formulation would have to be administered once a day which would result in better adherence, patient compliance, persistence, and associated economic impact. [11, 12]

Worldwide public health efforts to address a variety of chronic conditions are being undermined by an alarmingly low adherence to therapies. Non-adherence is a serious problem in patients on long-term treatment, accounting for up to 50% of cases where drugs fall short of their therapeutic goals. For non-adherent patients, the benefits of extended duration of treatment may not be sufficiently apparent. Adherence problems are prevalent where self-administration of treatment is required, including acute and chronic illnesses, a prominent disease being diabetes. And once daily dosing might be of great importance in resource-limited settings.

Current marketed therapies have to be administered twice a day either alone or in combination. Considering patient compliance, the present therapies fall short in addressing the problem pertaining to adherence to oral therapies. Further, from a health economic perspective, higher adherence rates with once-daily dosing relative to multiple dosing in a number of conditions were consistently associated with corresponding lower costs of health care resources utilization The twice-daily regimen has difficulty with medication adherence, increased cost of therapy, and possibility of more side effects. [14]

Sustained and or extended-release formulations keep the therapeutic dose at a steady level in the body for longer periods of time. Though they typically have a slightly slower onset compared to their immediate release counterparts, however, they maintain a more consistent level of the drug in the body, Hence, better treatment outcomes for longer periods of time while also lowering the occurrence of side effects with improved patient compliance can be achieved.[15]

The proposed project further provides a process of preparing formulations like solid dispersion or complexation and or tablet dosage form comprising of Dipeptidyl peptidase- IV (DPP-IV), SGLT-2 inhibitors, GLP-1 agonists and or alpha glucosidase inhibitors or a pharmaceutically acceptable salt thereof with at least one hydrophilic polymer, and pharmaceutically acceptable excipients. [16-18]

This project seeks to address the need for selection and characterization of a sustained and or extended-release polymers based on viscosity, functional group content, molecular weight, and such other important variables affecting the release characteristics.

8. Research Methodology

8.1 Formulation of oral composition containing Antidiabetic drugs

8.1.1. Standardization of drugs

Standardization with the help of techniques such as Fourier transform infra-red (FT-IR), UV visible spectroscopy, differential scanning calorimetry (DSC) and High-performance liquid chromatography (HPLC).

8.1.2 Stability indicating analytical method and Bioanalytical method development

Analytical method will be developed for analysis and standardization of drug for in vitro experiments of analysis of drug release. Stability indicating aspect of analytical method i.e. ability to quantify the

active in presence of its degraded products will be studied. Bioanalytical method for drug will be developed for chemical analysis of in vivo bio distribution study.

8.1.3 Screening of excipients for formulation

Various hydrophilic and hydrophobic polymers, copolymers will be screened. Selected excipients will be studied for drug excipient compatibility.

8.1.4 Formulation by Quality by Design approach

Based upon the screening studies, at least one high molecular weight hydrophilic polymer, and optionally one or more pharmaceutically acceptable carriers will be explored by Quality by Design approach. With hydrophilic polymers with specific viscosity ranges results in a synergetic pharmaceutical composition with desired stability, therapeutic effects and compact form.

8.1.5 Optimization of formulation using design of experiments (DoE)

Attempts will be made to optimize the formulation using DoE studies for achieving desired form, drug loading and desired level of stability, dissolution rates, and compact dosage form.

8.2 Characterization of API and formulations

8.2.1 Formulations will be evaluated for various characteristics like

a. Particle size and particle size distribution: The particle size distribution of the APIs and excipients will be analyzed.
b. Assay: The assay of oral formulation will be determined using HPLC.
c. Dissolution studies and Disintegration studies: The drug dissolution and disintegration studies will be determined using dissolution tester and disintegration tester.
d. Differential scanning calorimetry (DSC): The DSC studies of oral formulation will be carried to understand the stability and interaction between the drugs.
e. X ray diffraction studies - The X ray diffraction studies of oral formulation will be carried to understand the stability and interaction between the drugs.

8.2.2 Estimation of safe dose in experimental animals by oral route

Acute toxicity studies will be performed by oral route which is intended route of administration in experimental animals. This oral formulation will be tested will be tested for biocompatibility.

8.2.3 Characterization of the in vitro efficacy of anti-diabetic formulations

Antidiabetic activity will be performed with the help of DPP-IV inhibition assay, Inhibition of Alpha-Amylase Enzyme, and Glucose diffusion assay.

8.2.4 Characterization of in vivo efficacy and biodistribution of formulation after oral delivery

Attempts will be made to perform pharmacokinetics studies, in vivo efficacy and biodistribution studies by selection of suitable preclinical invivo model.

8.3 Stability studies according to ICH guidelines

The stability of developed formulation will be assessed by subjecting the formulations to different temperature and humidity conditions for a period of 6 months. Samples will be withdrawn periodically and analyzed for dissolution, disintegration, and in vitro release behavior.

Study timelines

1. Literature Survey	2 months
2. Procurement of drug and Excipients	2 months
3. Preformulation studies	2 months
4. Analytical Method Development	3 months
5. Formulation development and Optimization	9 months
6. Evaluation and characterization of the formulation	3 months
7. In vitro efficacy studies - action mechanisms of active ingredients on biological systems and their release	2 months
8. In vivo efficacy studies – Pharmacokinetics and efficacy studies	2 months
9. Stability studies	6 months
10. Study analysis, report and thesis writing	2 months

9. Statistical plan

The formulation will be optimized using Design Expert software with predefined quality target product profile and critical quality attributes. Various quantitative and qualitative tools like parametric and non-parametric tests including ANOVA, t-test will be used to analyze the results. Software like GraphPad prism will be used for statistical analysis of data.

10. Limitations of the study

Extrapolation of the data generated from in vivo animal studies may be difficult to carry out in higher animals and humans.

11. Expected outcomes

Stable, safe and effective oral formulation with desired therapeutic activity, improved drug response with maximum absorption/bioavailability, Cost effective, and affordable oral dosage form with societal impact.

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